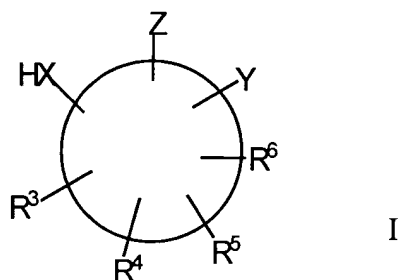


AMENDMENTS TO THE CLAIMS

The present amendment cancels claims 36-38. According to 37 C.F.R. § 1.121(c), after entry of the present amendment, the following claims are in the case:

1. (Previously Presented) A method of
 - a) synthesis of a linear or cyclic peptide,
 - b) synthesis of a C-terminal modified peptide, or
 - c) on-resin cyclisation of a peptide molecule, comprising the step of linking a cyclic aromatic or alkyl auxiliary compound of General Formula I to an amine nitrogen atom



in which the ring optionally comprises one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur;

is of 5 to 7 atoms;

comprises 3 carbon atoms substituted respectively by XH, Z, and Y; and

is additionally substituted by groups R^3 and R^4 when the compound is a 5-membered ring, or is additionally substituted by groups R^3 , R^4 , and R^5 when the compound is a

6-membered ring, or is additionally substituted by groups R^3 , R^4 , R^5 and R^6 when the compound is a 7-membered ring, in which

X is oxygen, sulphur, $\text{CH}_2\text{O}-$, or $\text{CH}_2\text{S}-$;

Y is an electron-withdrawing group;

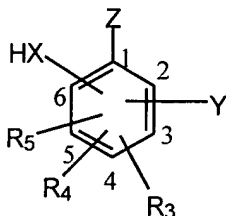
Z is any group which allows the formation of a covalent carbon-nitrogen bond;
and

R^3 , R^4 and R^5 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, alkoxy, aryloxy, XH or Y, or a covalent linkage to a solid support, and
in which R^3 and R^4 , R^4 and R^5 , or R^5 and R^6 can optionally together with the ring form a 5-, 6-, or 7-membered ring, thereby to facilitate conversion of the amine to an amide.

2. (Original) A method according to claim 1, in which Y is nitro, ketone, carboxylic ester, amide, nitrile, sulfonamide, sulfoxide, sulfone, sulfonate, fluoride, chloride, bromide or iodide.
3. (Previously Presented) A method according to claim 1, in which Z is an aldehyde, alkylalcohol, alkylhalide, or a ketone, or is a halogenated C_{1-3} alkyl group.
4. (Original) A method according to claim 3, in which the halogenated alkyl group is a methyl group.

5. (Previously Presented) A method according to claim 4, in which the halogen is iodine, bromine or chlorine.

6. (Previously Presented) A method according to claim 1, in which the auxiliary compound is of general Formula II



II.

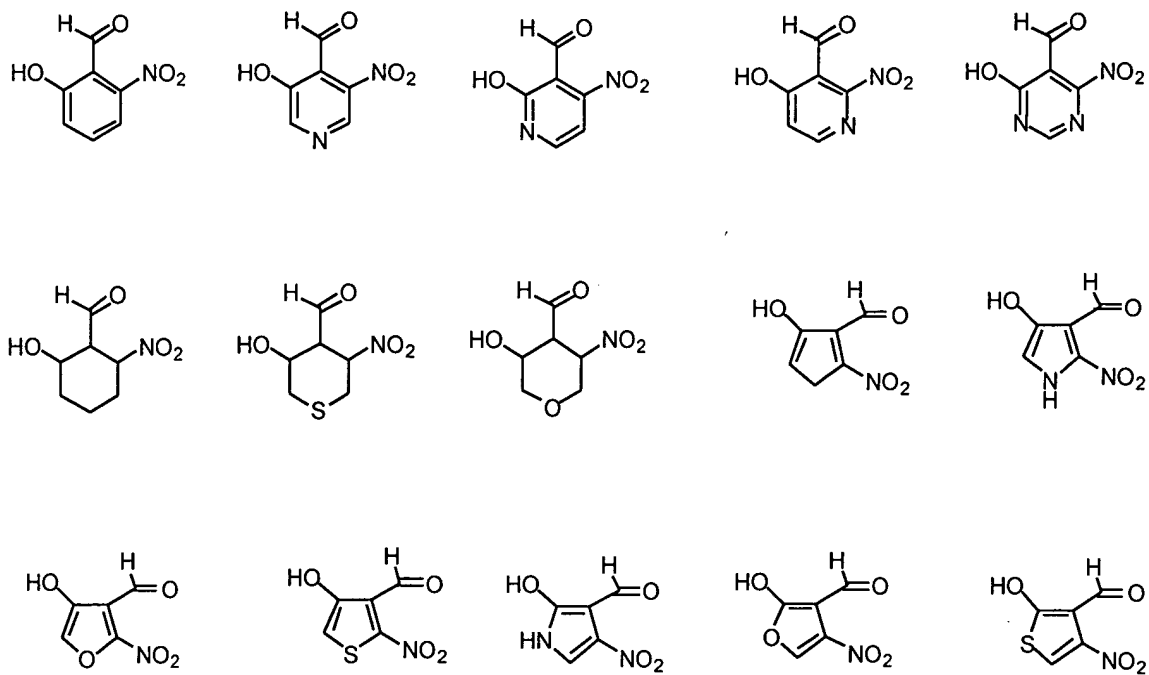
7. (Previously Presented) A method according to claim 1, in which the XH group is at position 2 or 3 in General Formula I or General Formula II, and Y is at any other position.

8. (Original) A method according to claim 7, in which the XH group is at position 2.

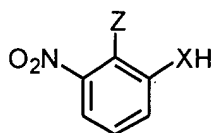
9. (Previously Presented) A method according to claim 7, in which Y is at position 6.

10. (Original) A method according to claim 9, in which Y is NO₂.

11. (Previously Presented) A method according to claim 1, in which the auxiliary compound is selected from the group consisting of



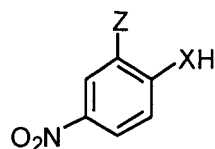
12. (Original) A method according to claim 1 for synthesis of a cyclic peptide, a large peptide, or a difficult peptide, in which the auxiliary compound is of General Formula III



III

and the auxiliary compound is removed by photolysis following amide bond formation.

13. (Original) A method according to claim 1 for synthesis of a cyclic peptide, a large peptide, or a difficult peptide containing one or more substituted amide bonds, in which the auxiliary compound is not removed, and the auxiliary compound is of General Formula IV



IV

14. (Original) A method of

- a) synthesis of a compound selected from the group consisting of linear and cyclic peptides, large peptides with a native peptide backbone, and “difficult” peptide sequences,
- b) backbone linkage for the synthesis of peptides, C-terminal modified peptides, or
- c) on-resin cyclisation,

comprising the step of linking a cyclic auxiliary compound of General Formula I, General Formula II, General Formula III, or General Formula IV to an amine nitrogen atom, thereby to facilitate conversion of the amine to an amide.

15. (Original) A method according to claim 14, in which XH in General Formula III is at position 2, and Y is NO₂ at position 6.

16. (Previously Presented) A method according to claim 1, in which R^3 , R^4 , R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, and a covalent linkage to a solid support.
17. (Previously Presented) A method of synthesis of a cyclic peptide, comprising the steps of
- synthesising a linear peptide to be cyclised,
 - linking an auxiliary compound as defined in claim 1 to a desired primary amine of the linear peptide,
 - activating a desired carboxylic acid to effect cyclisation, and where necessary inducing ring contraction, and optionally
 - removing the auxiliary compound after complete N acylation.
18. (Original) A method according to claim 17, in which ring contraction is induced by heating or by addition of a metal.
19. (Previously Presented) A method according to claim 17, in which the auxiliary compound is of General Formula III, and the auxiliary compound is removed by photolysis.
20. (Previously Presented) A method according to claim 17, in which steps a) to d) are performed on a solid support, and are followed by cleavage of the cyclic product from the solid support, and if desired, removal of side chain protecting groups.

21. (Previously Presented) A method according to claim 17, in which activation of the C-terminal carboxylic acid is performed in the presence of an auxiliary compound of General Formula III, and the cyclisation is performed by attaching the auxiliary compound to the desired amine via the Z-group.

22. (Previously Presented) A method of synthesis of a large peptide with a native peptide backbone, comprising the steps of

- a) synthesising a set of peptide fragments to be linked to form a large peptide,
- b) linking an auxiliary compound as defined in claim 1 to the primary amine of the first peptide fragment,
- c) activating the carboxylic acid of the second peptide fragment,
- d) adding the second peptide fragment to the first peptide fragment and forming a peptide bond between the two fragments, and optionally
- e) removing the auxiliary compound after N acylation is complete.

23. (Original) A method according to claim 21, in which the auxiliary compound is of General Formula IV, and the auxiliary compound is removed by photolysis.

24. (Previously Presented) A method of synthesis of a difficult peptide sequence, comprising the steps of

- a) linking an auxiliary compound as defined in claim 1 to one or more nitrogen atoms in peptide bonds of a peptide linked to a solid support,

- b) synthesising the complete peptide using standard solid phase synthesis methods, and optionally
- c) when synthesis is complete, removing the auxiliary compound.

25. (Original) A method according to claim 24, in which the auxiliary compound is of General Formula III, and the auxiliary compound is removed by photolysis.

26. (Previously Presented) A method of backbone linkage for synthesis of a linear peptide, comprising the steps of

- a) using an auxiliary compound as defined in claim 1 as a linker linking the α -nitrogen of an acid residue in the desired peptide to a solid support,
- b) assembling the linear peptide using standard solid phase peptide synthesis methods, and optionally
- c) removing the side chain protecting group(s), and/or
- d) cleaving the peptide from the solid support.

27. (Original) A method according to claim 26, in which the carboxylic acid group of the C-terminal amino acid residue is replaced by a functional group.

28. (Original) A method according to claim 26, in which the carboxylic acid group of the C-terminal amino acid residue is replaced by an ester, alkylalcohol, acetal or amide group.

29. (Previously Presented) A method according to claim 26, in which Y is nitro in position 6, XH is in position 2, and cleavage is performed by photolysis.

30. (Previously Presented) A method of on-resin cyclisation of a linear peptide, comprising the steps of

- a) using an auxiliary compound as defined in claim 1 as a linker linking the α -nitrogen of an amino acid residue in the desired peptide to a solid support,
- b) synthesising a linear peptide on a solid support, using standard solid phase peptide synthesis methods,
- c) deprotecting the desired amine and carboxylic acid groups,
- d) activating the carboxylic acid group to perform cyclisation, and optionally
- e) deprotecting amino acid side chain groups, and/or
- f) cleaving the cyclic peptide from the solid support.

31. (Original) A method according to claim 30, in which Y is a nitro group in position 6, XH is in position 2, and cleavage is performed by photolysis.

32. (Previously Presented) An auxiliary compound according to the General Formula as defined in claim 1, linked to a support suitable for solid phase peptide synthesis.

33. (Original) An auxiliary compound linked to a support, as defined in claim 32, in which the support is selected from the group consisting of functionalised polystyrene resins, tentagel resins, and polyethyleneglycol resins.

34. (Previously Presented) A kit for use in synthesis of a peptide, cyclic peptide, comprising:
- a) an auxiliary compound as defined in claim 1, or
 - b) an auxiliary compound as defined in claim 1, linked to a solid support, together with one or more reagents for solid phase peptide synthesis.
35. (Previously Presented) A method according to claim 15, in which R^3 , R^4 , R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, and a covalent linkage to a solid support.

Claims 36-38 Cancelled

RESPONSE

I. Correspondence Address

Applicants thank the examiner for forwarding a copy of the Requirement via facsimile, as the Requirement was originally mailed to Applicants' representatives' former address. Applicants' representatives' had earlier followed all proper procedures to ensure that the correct correspondence address was of record, and this has now been acknowledged by the Office.

II. Restriction Requirement

The Requirement has taken the position that the pending claims are drawn to two inventions that are allegedly not linked so as to form a single general inventive concept under PCT Rule 13.1. The inventions are set forth as:

- Group I: Claims 1-31 and 35, said to be drawn to a method of synthesis of a linear or cyclic peptide, or a C-terminal modified peptide or on-resin cyclization of a peptide molecule using an auxiliary compound of General formula I, comprising the step of linking a cyclic aromatic or alkyl auxiliary compound of General formula I to an amide nitrogen atom of the peptide; and
- Group II: Claims 32-34 and 36-38, said to be drawn to an auxiliary compound of General formula I, II, III or IV or a kit for use in synthesis of a peptide, cyclic peptide, comprising the auxiliary.

The class and subclass of the inventions are not set forth.

III. Unity of Invention

As indicated in the Requirement, the appropriate standard for assessing the claims of the present application is unity of invention under PCT Rules 13.1 and 13.2. Rule 13.1 requires that the claims be linked so as to form a single general inventive concept, and Rule 13.2 requires that there be a technical relationship between the claims involving one or more of the same or corresponding special technical features.

All claims were held to have unity of invention during the PCT examination phase, thus indicating a technical relationship between all claims involving one or more of the same or corresponding special technical features. As indicated in the Preliminary Amendment of record, all claims were also held to be novel and inventive during PCT examination. Aside from these findings, the Office has chosen to enter a restriction requirement in the present case.

IV. Election

Despite the unity of invention established during PCT examination, Applicants presently elect the Group I invention without traverse. Applicants reserve the right to pursue claims of the non-elected invention in a divisional or other application claiming priority to the present case.

V. Claims 32-34

The Office takes the position that the claims of Group I and Group II lack the same or corresponding special technical features as the auxiliary compound of Formula IV in Group II is allegedly known in the art in U.S. Patent No. 3,704,246 (Requirement bridging pages 2 and 3). This is addressed substantively below.

In terms of the restriction, claims 32-34 of Group II have the same or corresponding special technical features as the claims of the Group I invention. This is evident as independent claim 32 recites "an auxiliary compound according to the General Formula as defined in claim 1" and independent claim 34 recites "an auxiliary compound as defined in claim 1" (emphases added). Accordingly, claims 32-34 are properly included in the Group I invention and have been maintained as such.

VI. Further "Selections"

The Requirement further indicates that Applicants are also required to make several further "selections". In particular, to select an aromatic or cyclic alkyl structure, one ring size,

one heteroatom or carbon in the ring structure, and one functional group for each X, Y and Z from claim 1 (Requirement at page 2).

The Requirement at page 2 indicates that these "selections" are not species elections. As all such "selections" are all to be made from the elected invention, Applicants therefore assume that such "selections" reflect sub-species as an initial point for search and examination. Without agreeing with the propriety for requiring such selections, Applicants hereby select the following:

a ring size of 6 atoms;

the ring is all-carbon;

X is oxygen;

Z is carbonyl; and

Y is nitro.

VII. U.S. Patent No. 3,704,246 is Distinguished

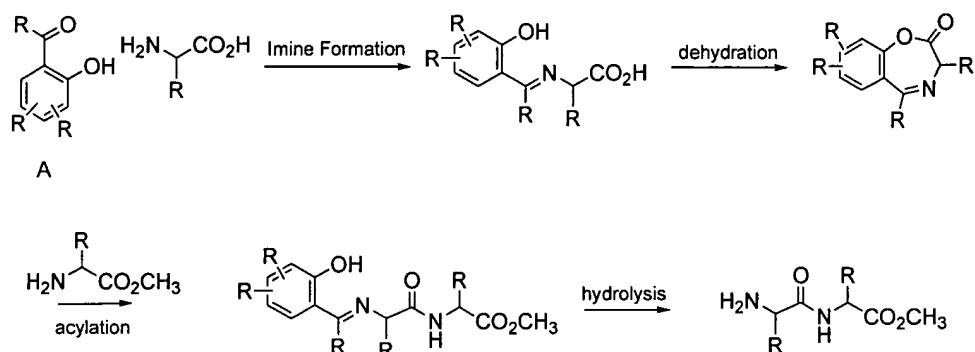
The Requirement at page 3 takes the position that the auxiliary compound of Formula IV, from the Group II invention, is known in the art and cites U.S. Patent No. 3,704,246 ("the '246 patent"). The '246 patent does not anticipate or render the claimed invention legally obvious.

The '246 patent relates to a method for the production of peptides, comprising the steps of protecting the free amine group of an amino acid, condensing the acid-alcohol to the lactone, forming a peptide bond using an amino acid ester, and deprotecting the amine function of the thus-obtained derivative.

In the process of the '246 patent, the amino acid is protected by production of a Schiff base of an amino acid and a compound of formula A (see the scheme below in which R, for example, is hydrogen or a lower alkyl group, preferably methyl, and R1 and R2 are independently hydrogen, a halogen, a nitro group, or together form an aromatic ring). The

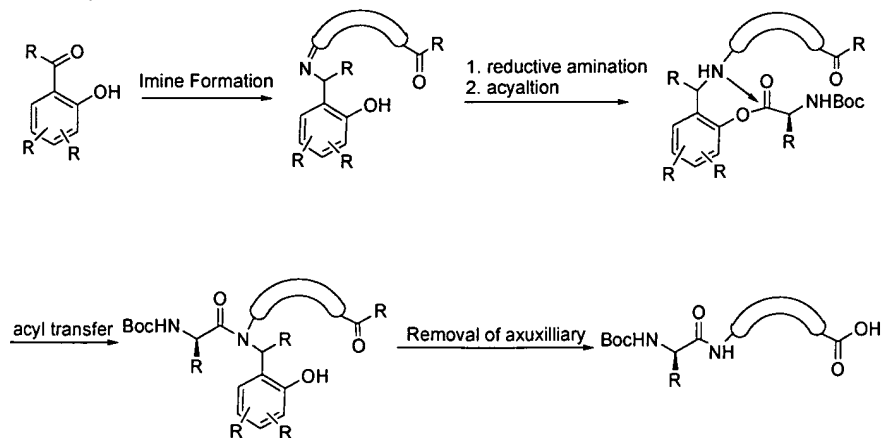
compound of formula A in the '246 patent consequently acts as a protecting group, and is not involved in formation of an amide bond, *i.e.*, the formation of a peptide bond. After amide bond formation, the compound of formula A is removed, to yield the unprotected amine.

Peptide Formation



In contrast, in the methods of the presently claimed invention, the compound of general formula A, *i.e.*, the auxiliary, forms a Schiff base and then undergoes reductive amination to form a single bond, followed by *O*-acylation and then an *N-to-O* acyl shift to generate the tertiary amide bond, *i.e.*, it acts to facilitate a further reaction. The auxiliary is preferably then removed by photolysis. This is illustrated in the following flow chart:

An example of Amide Bond Formation



Therefore, there are many key differences between the '246 patent and the presently claimed invention, including the following points.

1) amide bond formation occurs at the "*opposite ends*" of the molecule. The present invention requires amide bond formation to occur at the N-terminus, while use of the compounds described in the '246 patent results in amide bond occurring at the C-terminus.

2) the method of the present invention uses an auxiliary that has a strong accelerating effect on the acylation rate of the nitrogen atom. For compounds mentioned in the '246 patent, the benzaldehyde derivatives were used as a protecting group, and the resultant imine nitrogen was not involved in the acylation process.

3) the present invention involves a secondary *amine*, a moiety with a different bond order to that of compounds mentioned in the '246 patent. In the compounds within the '246 patent, an *imine* was the respective product.

4) the present invention requires that the secondary amine is functionalized, while in the '246 patent, compounds of the nitrogen imine were not functionalized.

5) the present invention relates to the synthesis of peptides, linear and cyclic peptides. The '246 patent refers primarily to linear peptides and more specifically to dipeptides.

6) for synthesis of a linear peptide, the present invention requires the formation of an ester group that is formed by the addition of an activated protected-amino acid to the auxiliary-amino acid group. In compounds mentioned in the '246 patent, an internal lactone is formed.

Therefore, the presently claimed invention is novel and non-obvious over the '246 patent.

VIII. Amendment to the Specification

Applicants have noticed that there was a clerical error in the formula at page 14 of the specification. The listed formula was incorrectly given as formula IV, instead of the stated formula I, which clerical error is now corrected by amendment to insert the proper formula I.

One of ordinary skill in the art would recognize that there was an error in the formula at page 14 and would readily appreciate the appropriate correction. Both the error and the appropriate correction would be clear, for example, by comparing page 14 to page 17 and to claims 1 and 13. In particular, noting that the correct formula for general formula I is that depicted in claim 1, and that formula IV was incorrectly depicted, as in claim 13. It is thus clear that the inclusion of formula IV at page 14 was the result of a clerical error.

The correction of the formula at page 14 of the specification is proper, as one of ordinary skill in the art would not only recognize the existence of the error in the specification, but would also appreciate the appropriate correction. *In re Oda*, 170 USPQ 268 (CCPA 1971). See also, MPEP 2163.07, describing amendments that are NOT new matter (emphasis as in original; MPEP, February 2003, page 2100-177, column 2). Therefore, the amendment to page 14 of the specification does not constitute new matter.

IX. Status of the Claims

Prior to the present Requirement, claims 1-38 were in the case. Presently, claims 36-38 have been canceled without traverse as drawn to a non-elected invention. No claims have been amended or added. Claims 1-35 are therefore in the case. In accordance with 37 C.F.R. § 1.121, the pending claims are listed in the amendment section.

X. Conclusion

This is a complete response to the referenced Requirement. The response is timely filed and no fees should be required. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be deemed necessary, Applicants respectfully request a telephone call to the undersigned representative to discuss deduction from Applicants' representatives' Deposit Account No. 50-0786/4050.001100.

All claims are believed to be in condition for allowance and an indication to this effect is respectfully requested. Should the Office have any questions, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,
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Date: August 25, 2004